The cardiorenal syndrome

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ABSTRACT **The progress made in the medical and device therapy of chronic heart failure (CHF) due to left ventricular systolic dysfunction has heralded new problems. Patients present having survived longer with CHF, but with minimal exercise reserve and renal dysfunction with or without systemic congestion. We now recognise this clinical presentation as the cardiorenal syndrome. The classic hemodynamic/neurohormonal understanding of the syndrome explains only partly the pathophysiology, and it is now recognised that the kidney early on in a heart failure patient shows abnormal handling of a sodium load and changes in renal blood flow. Renal dysfunction is commonly seen in patients with CHF and the higher the level of the admission serum creatinine as well as an increase in serum creatinine during hospitalisation portends a graver prognosis. Chronic kidney disease itself is associated with a greater incidence of heart failure, but unravelling the pathophysiological mechanisms involved in this reciprocal relationship between the heart and the kidneys remains elusive. Essentially the problem remains in trying to maintain optimal fluid balance while preserving renal function.** SAHeart 2008; 5:124-127

INTRODUCTION

Most doctors who treat patients suffering from chronic heart failure (CHF) caused by left ventricular systolic dysfunction recognise the "wet or dry", cold patient presenting with minimal reserve on effort and renal dysfunction with or without hyponatremia. Our "success" in treating CHF with angiotensin converting enzyme inhibitors and beta-blockers has meant that more patients survive into the later stages of the disease. The clinical challenge ironically then retrogresses to one that involves optimal fluid balance while preserving renal function. What we may not realise is that the underlying pathophysiology of this "terminal phase" of CHF is poorly understood. The management thereof can be an emotionally and cognitively demanding saga and ultimately there is no consensus amongst the "experts" as to its appropriate care. The cardiorenal syndrome in CHF results from major aberrations in the mutually beneficial interaction between heart and kidney. It can be seen as a complex interaction between the heart, kidney and vasculature.

DEFINITION

The cardiorenal syndrome is defined as "worsening renal function that limits diuresis despite obvious clinical volume overload." This syndrome limits effective CHF therapy, prolongs hospitalization and has significant prognostic implications. It predicts an increased rate of death and rehospitalization. The clinical picture of CHF relates to congested organs and hypoperfused tissues, exemplified by the cardiorenal syndrome.

The definition of worsening renal function remains controversial, with suggestions including a 26.5 umol/l increase in serum creatinine (SCr) above baseline, a rise in SCr above a threshold (221 umol/l), a percentage increase from baseline (>25%), or a combination of these factors.[1,2] Whatever the definition, clinically this syndrome is not difficult to recognise – the challenge is to find effective therapies and management strategies. Seventy percent of patients admitted for acute deteriorating heart failure have decreased renal function and 20-45% will experience an increase in SCr in excess of 26.5 umol/l while in hospital.[3] Glomerular filtration rate (GFR) measures the filtration capacity of the kidneys and is considered the best overall index of renal function. GFR is usually estimated by creatinine-based equations that incorporate demographic characteristics, such as age, gender, race and weight to account for differences in muscle mass and hence creatinine generation. The formulae that we use to estimate GFR have their problems[4] and require cautious interpretation in daily practice. The variance is wide, at approximately 30 ml/min per 1.73 m^2. The Cockroft-Gault formula developed in males with steady state creatinine and first described

in 1976[5] with an arbitrary correction for females tends to overestimate GFR in the lower ranges. It is recommended that it not be used for prognostic purposes. The Modification of Diet in Renal Disease (MDRD) equation developed predominantly in males with chronic kidney disease without diabetes mellitus is an improvement, but underestimates GFR in healthy people. However, it is more precise, especially in the lower ranges of GFR and was felt to be the most reliable in clinical practice.[4] This formula includes an adjustment for black individuals, allowing for their increased muscle mass.[6] Both these formulae can be used very well for pharmacokinetic purposes. Interestingly, serum creatinine measurements can vary between laboratories. We may therefore still require newer markers of GFR with cystatin C being used as a future good measurement of renal function.[7]

There are 5 classes in the classification of the cardiorenal syndrome (Table 1), but this article will concentrate on Class II, although this can be difficult to differentiate from Class IV.

THE HEART AND THE KIDNEY

The heart and the kidney are closely linked as regards physiological health. The heart is required to pump blood at a rate commensurate with the requirements of the metabolising tissues. The greatest responsibility for solute and water excretion is borne by the kidney. With normal functioning kidneys, approximately 180 litres of fluid is filtered per day, yet only 2 litres are usually excreted. This underlines the great deal of work that the kidney performs, yet it only receives 19% of the cardiac output at rest and 3% with strenuous exercise. An increase in plasma volume is usually associated with increased sodium and water excretion by the kidneys. Paradoxically, in CHF sodium and water are retained despite an increase in plasma volume.[8]

CLASSIC UNDERSTANDING

The classic understanding of the heart-kidney interaction in heart failure is based on an amalgamation of the hemodynamic and neuro-hormonal approaches to understanding the syndrome.[8] Left ventricular systolic dysfunction results in decreased cardiac output, which sets up the activation of the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous and the natriuretic peptide systems. Via diminished renal blood flow and perfusion, structural renal changes occur that impair renal function and, together with neuro-hormonal activation, causes increased water and sodium retention, vasoconstriction and diminished cardiac performance. These adaptive mechanisms fail to normalise cardiac output including the cost of an increased circulating plasma volume, which then further amplifies the downward spiral of heart failure begetting heart failure. Diuretic resistance ensues and the cardiorenal syndrome is "born".

TABLE 1: Classification of the cardiorenal syndrome

Class I	Acute cardiac disease affecting renal function
Class II	Chronic cardiac disease causing renal disease
Class III	Acute renal disease affecting cardiac function
Class IV	Chronic renal disease causing cardiac disease
Class V	Secondary cardiorenal syndrome (CRS)

EARLY SIGNS OF CARDIO-RENAL INTERACTION

Deranged sodium handling

The classic concepts of the cardiorenal syndrome may be dissolving. Volpe et al.[9] described the effects of increased sodium intake on GFR, renal plasma flow and renal vascular resistance in mild asymptomatic HF. In both normal and mild heart failure subjects, the increased sodium intake (250 mmol/day vs. 100 mmol/day) caused GFR and renal plasma flow and filtered load of sodium to increase significantly and renal vascular resistance to drop but, while the fractional clearance of water, excretion of potassium and sodium increased in normal subjects, it was significantly reduced in the mild CHF group. These CHF patients had no clinical signs or symptoms of congestion. This inability to excrete a volume load precedes any evidence of reduced cardiac output. Importantly, after the addition of low doses of enalapril these effects were reversed and "normalised" the response of the mild CHF group to an increased sodium load. Despite normal hemodynamics and increased filtered sodium, less sodium was excreted, implying that abnormal sodium retention is seen early in CHF, relating to an abnormality of proximal tubular sodium handling (distal delivery of sodium is decreased in CHF) which is undetectable during normal sodium intake. Enalapril increases the distal delivery of sodium.

Altered glomerular hemodynamics

A test of renal hemodynamic reserve (the angiotensin II / nitric oxide balance) involves the assessment of the glomerular vasodilatory response to an amino acid infusion. In another interesting study, Magri et al.[10] infused amino acid into normal and mild asymptomatic CHF patients. Normally, an amino acid infusion will reduce renal vascular

resistance and increase GFR. GFR, effective renal plasma flow increased and renal vascular resistance decreased in the normal subjects but not the CHF group. Only after 6 weeks of enalapril (5mg) or losartan (50 mg) administration at 20h00 (without affecting basal systemic or renal hemodynamics) was the "normal response" elicited in the CHF group. The early loss of renal functional reserve in CHF appears to relate in part anyway, to local angiotensin II production and the intricate balance between angiotensin II and nitric oxide. This led the investigators to conclude that reduced ejection fraction is a poor predictor of cardiac output and renal blood flow and that aberrations in the intra-renal renin-angiotensin-aldosterone axis are present early, before the so-called classic theory of hemodynamic compromise plays a role.

Further detracting from the classic theory is the work of Stevenson and Tillisch.[11] In a short-term hemodynamic study in CHF and performed in the resting state, they showed that stroke volume is often maximal and can be maintained after reducing LV filling pressures to normal while keeping systemic vascular resistance stable. During exercise, more volume reserve may be required. This tends to underline too, the different hemodynamics present in acute heart failure vs. CHF. In acute heart failure, filling pressures need to be maximised to maintain stroke volume, but in the chronically dilated heart LV filling pressures and ventricular volumes cannot be equated. High ventricular volumes can be maintained with normal filling pressures.

PREVALENCE

Large HF interventional trials (SOLVD Prevention (SOLVD-P),[12] SOLVD Treatment (SOLVD-T))[13] have shown that the blood urea/creatinine ratio (indicating a pre-renal component to the renal dysfunction) is slightly, but significantly lower in those with moderate renal insufficiency than those without. In the Treatment trial, no significant difference in this ratio was seen in those with and without renal insufficiency.[1] Interestingly 21% of 3 673 patients in the SOLVD-P trial had a GFR < 60 ml/min. This figure is all the more remarkable, as the patients in this trial were NYHA FC I –II. In the SOLVD-T trial, 35% of 2 161 patients had a GFR < 60 ml/min and these were majority Class II patients.[14] In "real life" renal dysfunction may be more common as this category of patient is often excluded from trials. Overall a serum Creatinine > 132 umol/l and a GFR < 60ml/min is seen in approximately 50% of CHF patients.

All this tends to underline the fact that renal dysfunction occurs early in CHF before hemodynamic insults, patients often have preceding decline in GFR before presenting in clinical CHF, implying shared risk factors for 2 independent conditions, but as CHF worsens so does the degree of renal dysfunction. General arteriosclerosis is highly correlated with severity of glomerulosclerosis and of renal arteriosclerosis, probably explaining the difference in prevalence of renal dysfunction amongst different population groups.[6] As a contrast to predominantly "western" patients, in a retrospective analysis of 163 Black African patients with predominantly NYHA FC II/III CHF, only 12% had an eGFR < 60ml/min.[6] This prevalence is considerably lower than that reported in the SOLVD trials. The average age of the South African cohort was younger (48yrs) and concomitant atherosclerotic disease was in all likelihood low, although this was not formally assessed in the analysis. As seen in the recently published CORONA study,[15] the mean entry SCr was 115 umol/l with 24% of entrants having SCr > 130 umol/l. The mean estimated GFR was < 60 ml/min indicating that the majority of patients in CORONA would be classified as having Stage 3 chronic kidney disease. This is despite the mean entry blood pressure being 129/76 and 37% of entrants being NYHA FC II. As has been previously noted,[12] depressed renal function does not appear to be characterized by a low-output state as a significant number of these patients present with elevated blood pressure. Not only is there an association of 2 independent conditions, but a calculated creatinine clearance of < 60 ml / min is independently associated with all cause death, pump failure death and heart failure hospitalizations.

Chronic kidney disease can be seen as catalyst to the development of CHF[16] and CHF itself is also an important aggravating factor for further renal dysfunction by various mechanisms, not all currently understood. According to the NHANES data, 28% of patients with renal dysfunction have CHF. What is clear, however, is that the classical hemodynamic theory is inadequate to explain (especially in the early phase) the entire cardiorenal syndrome. What appears more pertinent is that LV systolic dysfunction is associated early on with renal dysregulation that is not related to altered hemodynamics primarily, but rather to intra-renal AII/NO imbalance. Adequacy of baseline renal function is an important determinant involved in the progression to the cardiorenal syndrome and the maintenance of good renal function delays progression from LV systolic dysfunction to frank CHF. Once CHF is established, then hemodynamic, inflammatory, and oxidative stressors all play a role together with effects of medication, salt and fluid restriction.[17]

PROGNOSIS

Pathophysiological mechanisms underlying this reciprocal relationship between the heart and kidneys are still enigmatic.[18] Renal failure increases cardiovascular mortality in HF patients by up to 1% per each 1ml/min decrease in creatinine clearance.[3] Although renal dysfunction predicts all-cause mortality, it is most predictive of death from progressive heart failure. In the ADHERE registry,[19] patients presenting with reduced LV systolic function CHF and SCr < 176umol/l had an in-hospital mortality of 2.9%, but those presenting with SCr > 176 umol/l had an 8.4% mortality. Not only was baseline SCr predictive of mortality, but an increase during hospitalization further worsened prognosis. Autoregulation of renal perfusion is effective down to a systolic BP of 90 mmHg and/or a cardiac index of 1.5. The decline in renal function however is often worse when hypotension is associated with venous congestion as the renal filtration gradient is further reduced.

We have made great strides in the pharmacological management of chronic HF over the last 3 decades. Importantly, however, although we prolong survival with drugs, eventually the patient deteriorates[20] and we are increasingly presented with a very ill patient, hypoperfused, dyspnoeic and with significant and progressive renal dysfunction.

As more patients survive into advanced stages of disease, it is increasingly difficult to maintain optimal fluid balance while preserving renal function. In the CORONA trial, despite 92% of patients being on an ACEI or ARB, 75% on a beta-blocker and 40% on an aldosterone antagonist, a third of all patients (from both arms of the trial) were dead by two and a half years.

CONCLUSION

The phenomenon of a cardiorenal limit to standard heart failure medications is becoming more obvious as the experience with HF lengthens. Much research needs to be done to further understand the pathophysiology of the cardiorenal syndrome. This may ultimately lead to improved therapy.

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